UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM:

Subject: EPA Reg. No.: 264-RRUR/Sivanto 200 SL
DP Barcode: 423560
PC Code: 122304

From: Marianne Lewis, Biologist
IVB3 Branch
Registration Division (7508P)

JCR

10/30/14

To: Venus Eagle, PM 01
IVB3 Branch
Registration Division (7508P)

Applicant: Bayer CropScience
P.O. Box 12014
2 T.W. Alexander Drive
Research Triangle Park, NC 27709

FORMULATION FROM EPA Reg. No. 264-RRUR LABEL:

	% by wt.
Active Ingredient(s):	
Flupyradifurone:	17.09%
Inert Ingredient(s):	82.91%
Total	100.00%

BACKGROUND: The registrant has submitted new acute toxicity to support the registration of their new product, EPA Reg. No. 264-RRUR. The MRID's are as follows: 488445-51 (81-1), 488445-52 (81-2), 488445-53 (81-3), 488445-54 (81-4), 488445-55 (81-5), 488445-56 (81-6). The studies were conducted by Bayer Schering Parma AG and Bayer CropScience. The test material used in each of the studies was the subject product, referred to in the studies as BYI 02960 SL 200.

RECOMMENDATIONS:

- The acute toxicity studies submitted are acceptable to support the registration of EPA Reg. No. 264-RRUR.

The acute toxicity profile for EPA Reg. No. 264-RRUE is currently:

Acute Oral	III	Acceptable
Acute Dermal	III	Acceptable
Acute Inhalation	IV	Acceptable
Primary Eye	III	Acceptable
Primary Dermal	IV	Acceptable
Skin Sensitization	skin sensitizer	Acceptable

NOTE: The acute toxicity requirements have been satisfied for the subject product.

DATA REVIEW FOR ACUTE ORAL TOXICITY (§81-1, 870.1100)

Product Manager: Venus Eagle, PM 01
MRID No.: 488445-51

Reviewer: Marianne Lewis
Study Completion Date: 6/17/10
Report No.: T 7081576

Testing Facility: Bayer Schering Pharma AG
Author: U. Gillissen

Quality Assurance (40 CFR §160.12): Included

Test Material: BYI 02960 SL 200, clear brown liquid

Species: Wistar rat
Age: young adult
Weight: females = 170 – 185 g
Source: Harlan GmbH

Conclusion: Acute Toxic Class Method

1. **LD_{50} (mg/kg):** > 2000 mg/kg

2. **Toxicity Category:** III **Classification**: Acceptable

Procedure (Deviations from §81-1): none

Results:

Test Sequence	Dose Level (mg/kg)	24 hours: number of deaths/number tested	48 hours: number of deaths/number tested
1	2000	0/3	0/3
2	2000	0/3	0/3

Observations: decreased motility & tremors

Gross Necropsy: no observable abnormalities

DATA REVIEW FOR ACUTE DERMAL TOXICITY (§81-2, 870.1100)

Product Manager: Venus Eagle, PM 01
MRID No.: 488445-52

Reviewer: Marianne Lewis
Study Completion Date: 6/17/10
Report No.: T 7081577

Testing Facility: Bayer Schering Pharma AG
Author: U. Gillissen

Quality Assurance (40 CFR §160.12): Included

Test Material: BYI 02960 SL 200, clear brown liquid

Species: Wistar rat
Weight: males = 285 – 295 g; females = 238 – 243 g
Age: young adult
Source: Harlan GmbH

Summary:

1. **LD_{50} (mg/kg):** > 2000 mg/kg

2. **Toxicity Category:** III **Classification:** Acceptable

Procedure (Deviations From §81-2): none

Results: **Reported Mortality**

Dosage (mg/kg)	(number deaths/number tested)		
	Males	Females	Combined
2000	0/5	0/5	0/10

Observations: Twenty four hours prior to application of the test material the dorsal area and trunks were clipped free of hair (approximately 10% of body surface area). The test material was applied to a wet 6 x 5 cm Cutiplast steril coated with air-tight leukoflex pad and placed on the intact test site. The pads were secured in place use Peha-Haft cohesive stretch tape and covered with a Lomir biomedical Inc rate jacket which was connected with a safety pin to the stretch tape to ensure that the animals could not ingest the test material. After 24 hours, the wraps and pads were removed and the test sites were gently cleansed with soap and water and patted dry. All appeared active and healthy for the duration of the study.

No observable abnormalities were noted

Gross Necropsy Findings: No observable abnormalities were noted.

DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (§81-3, 870.1300)

Product Manager: Venus Eagle, PM 01
MRID No.: 488445-53

Reviewer: Marianne Lewis
Study Completion Date: 6/17/10
Report No.: T 2080851

Testing Facility: Bayer Schering Pharma AG
Author: A. Folkerts

Quality Assurance (40 CFR §160.12): Included

Test Material: BYI 02960 SL 200, clear brown liquid

Species: Hsd Cpb:WU(SPF) rat
Weight: males = 231 – 245 g; females = 172 – 177 g
Age: young adult
Source: Harlan Labs

Summary:

1. **LC_{50} (mg/L):** females: 3.4 mg/L males: 4.4 mg/L

2. **MMAD:** 2.07 µm **GSD:** 1.88

3. **Tox. Category:** IV **Classification:** Acceptable

Procedure (Deviation From §81-3): none

Results: **Reported Mortality**

Exposure Concentration	(number deaths/number tested)		
	Males	Females	combined
1.956 mg/L	0/5	0/5	0/10
4.483 mg/L	2/5	4/5	6/10

Chamber Atmosphere		
Dose Level mg/L	MMAD	GSD
1.956	1.66 µm 1.66 µm	1.72 1.66
4.483	1.86 µm 2.07 µm	1.68 1.88

Chamber Environment	Dose Level mg/L	Dose Level mg/L
	1.956	4.483
Chamber Volume	3.8 L (nose only)	3.8 L (nose only)
Airflow (L/min)	15	15
Temperature (˚C)	22.9	22.8
Relative Humidity %	5.1	<6.0

Clinical Observations:

Dose mg/L	Time of Death	Clinical Observations
1.965	N/A	Bradypnea, labored breathing patterns, irregular breathing, piloerection, reduced motility, limp, high legged gait, serous nasal discharge, red encrustation on nostrils
4.483	2/10 on day 1 3/10 on day 2 1/10 on day 3	Bradypnea, labored breathing patterns, irregular breathing, piloerection, cyanosis, reduced motility, limp, high legged gait, serous nasal discharge, nose & muzzle with red encrustation, red encrustation on nostrils

Gross Necropsy Findings:

Dose mg/L	Gross Necropsy Observations
1.965	Dark red foci on lungs, discoloration of lungs, discolored kidneys
4.483	Reddened nasal mucosa, collapsed lung dark red, yellow foamy content in trachea, red mucosal content – intestines, light discoloration of spleen, red nasal discharge, bloated stomach, black liver, gray areas on lung, partially red mucosa, marked lobular pattern on liver, reddish liquid in trachea, reddish content in urinary bladder

DATA REVIEW FOR PRIMARY EYE IRRITATION TESTING (§81-4, 870.2400)

Product Manager: Venus Eagle, PM 01
MRID No.: 488445-54

Reviewer: Marianne Lewis
Study Completion Date: 2/25/10
Report No.: T 7081314

Testing Facility: Bayer Schering Pharma AG
Author: C.Gmelin

Quality Assurance (40 CFR §160.12): Included

Test Material: BYI 02960 SL 200, clear brown liquid

Dosage: 0.1 mL
Species: Crl:KBL(NZW)BR albino rabbit
Sex: 3 females
Weight: 2.5 – 2.6 kg
Age: young adult
Source: Charles River

Summary:

Toxicity Category: III

Classification: Acceptable

Procedure (Deviations From §81-4): none

Results:

Observations	(number "positive"/number tested)					
	Hours				Days	
	1	24	48	72	7	14
Corneal Opacity	0/3	0/3	0/3	0/3		
Iris	0/3	0/3	0/3	0/3		
Conjunctivae						
Redness	0/3	1/3	1/3	0/3		
Chemosis	0/3	0/3	0/3	0/3		

From 24 to 48 hours, 1/3 exhibited diffuse crimson red conjunctivae. All irritation had cleared by 72 hrs.

DATA REVIEW FOR SKIN IRRITATION TESTING (§81-5, 870.2500)

Product Manager: Venus Eagle, PM 01
MRID No.: 488445-55

Reviewer: Marianne Lewis
Study Completion Date: 6/17/10
Report No.: T 0081317

Testing Facility: Bayer Schering Pharma AG
Author: C. Gmelin

Quality Assurance (40 CFR §160.12): Included

Test Material: BYI 02960 SL 200, clear brown liquid

Dosage: 0.5 mL
Species: Crl:KBL(NZW)BR albino rabbit
Age: young adult
Sex: 3 females
Weight: 2.7 – 2.8 kg
Source: Charles River

Summary:

1. **Toxicity Category:** IV

2. **Classification:** Acceptable

Procedure (Deviations From §81-5): none

Results: Twenty four hours prior to application of the test material the dorsal area and trunks were clipped free of hair. The test material was applied to the intact test site (2.5 x 2.5 cm) under a gauze patch and held in place with non-irritant tape. After 4 hours the pads and wrappings were removed and the test sites were cleansed.

No dermal irritation was observed.

DATA REVIEW FOR DERMAL SENSITIZATION TESTING (§81-6, 870.2600)

Product Manager: Venus Eagle, PM 01
MRID No.: 488445-56

Reviewer: Marianne Lewis
Study Completion Date: 5/7/10
Report No.: SA 10101

Testing Facility: Bayer CropScience
Author: M.Repetto

Quality Assurance (40 CFR §160.12): Included

Test Material: BYI 02960 SL 200, clear brown liquid

Positive Control Material: alpha-hexylcinnamaldehyde

Species: CBA/J mouse
Weight: females = 17.4 – 23.7 g
Age: young adult
Source: Harlan Labs

Method: Local Lymph Node Assay

Summary:

1. **This Product is a** skin sensitizer

2. **Classification:** Acceptable

Procedure (Deviation From §81-6): none

Procedure: Five sets of 5 female mice were selected and placed in Groups: I (vehicle – 1% pluronic acid L92); II (25% test material in vehicle); III (50% test material in vehicle), and IV (100% test material) and V (positive control – 30% HCA in vehicle);. On days 0, 1, & 2 each group was treated 25 µL with its corresponding substance on the dorsum of both ears.

All animals were rested on days 3 & 4.

On day 5 all were injected in the tail vein with 250 µL of 0.01 M phosphate buffered saline, PBS, containing 20 µCi of [methyl, 1^{1}, $2^{1\text{-}3}$H]Thymidine. Five hours after injection, the animals were sacrificed, the draining auricular lymph nodes were excised and pairs from each individual animal were processed.

A single cell suspension was prepared by mechanical disintegration in PBS by crushing with plastic piston. The cell suspensions were transferred to a centrifuge tube and washed w/an excess of PBS and centrifuged for approx. 20 mins at 1800 rpm. This process was done twice. Each time the supernatant was decanted & discarded after centrifugation. After the second wash, was precipitated w/5% TCA (5 mL) at 3°C for overnight. The pellets were resuspended in 1 mL saline placed in ultrasonic bath to ensure a thoroughly dispersed suspension. This was then transferred into scintillation pots containing 19 mL of scintillation fluid. Incorporation of the tritiated thymidine was measured by liquid scintillation counting as disintegrations per minute (DPM) from the paired lymph nodes of each animal and a mean DPM/animal was calculated for each group.

Animal number	DPM Count	Test/Vehicle control ratio
Group I - vehicle control – 1% aqueous Pluronic Acid		
UT1F1941	1236	
UT1F1942	837	
UT1F1943	606	
UT1F1944	Not recorded – lab error	
UT1F1945	548	
Group II – 25% test material in vehicle		
UT2F1946	917	1.14
UT2F1947	Not recorded – lab error	--
UT2F1948	1221	1.50
UT2F1949	1056	1.31
UT2F1950	1024	1.27
Group III – 50% test material in vehicle		
UT3F1951	1085	1.34
UT3F1952	2634	3.26
UT3F1953	1875	2.32
UT3F1954	1701	2.10
UT3F1955	2170	2.68
Group IV - 100% test material in vehicle		
UT4F1956	1554	1.92
UT4F1957	1916	2.37
UT4F1958	2517	3.12
UT4F1959	3131	3.88
UT4F1960	2819	3.49

Group V – positive control (30% HCA)		
UT5F1961	2985	3.69
UT5F1962	2956	3.66
UT5F1963	5725	7.09
UT5F1964	4960	6.15
UT5F1965	9145	11.33

A positive response is defined as having a stimulation index (test/vehicle control ratio) of ≥3.0

LABELING:

ID #: 000264-RRUR BYI 02960 SL 200

SIGNAL WORD: **CAUTION**

HAZARDS TO HUMANS AND DOMESTIC ANIMALS:

Harmful if swallowed. Harmful if absorbed through skin. Causes moderate eye irritation. Avoid contact with eyes, skin, or clothing. Wear long sleeved shirt, long pants, shoes, socks, and chemical resistant gloves (such as or made out of any waterproof material, selection category A). Prolonged or frequently repeated skin contact may cause allergic reactions in some individuals.

FIRST AID:

IF SWALLOWED: Call a poison control center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to by a poison control center or doctor. Do not give anything by mouth to an unconscious person.

IF ON SKIN OR CLOTHING: Take off contaminated clothing. Rinse skin immediately with plenty of water for 15-20 minutes. Call a poison control center or doctor for treatment advice.

IF IN EYES: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.

Have the product container or label with you when calling a poison control center or doctor or going for treatment. You may also contact 1-800-xxx-xxxx for emergency medical treatment information.

USER SAFETY RECOMMENDATIONS:

User should wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet.

User should remove clothing/PPE immediately if pesticide gets inside. Then wash thoroughly and put on clean clothing.

Users should remove PPE immediately after handling this product. Wash the outside of gloves before removing. As soon as possible, wash thoroughly and change into clean clothing.